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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/283,431	04/01/1999	WEN-QIANG ZHOU	475.08.423	9988

7590 08/12/2004

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/283,431	ZHOU ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02-26-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 9, 2004 has been entered.

Double Patenting

Claims 4-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/291,058. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 4-11 are directed to oligonucleotides encompassed entirely in the claims of 10/291,058 and are directed to oligonucleotides which are disclosed in the co-pending case as the preferred embodiments of the claimed oligonucleotides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-6 are maintained as rejected and new claims 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metelev et al. (US patent No. 6,143,881) in combination with Ghosh et al. (reference B1 on PTO form 1449, filed April 24, 2000).

Claims 4-6 are drawn to oligonucleotides that consist of a region of deoxyribonucleotides that comprises alternating phosphodiester and phosphorothioate internucleoside linkages and one or more regions of 2'-O-substituted ribonucleotides, and further wherein the oligonucleotides comprise between 12 and 50 or 17 and 35 nucleotides. The specification discloses alternating to encompass any regular or irregular pattern of phosphodiester and phosphorothioate internucleoside linkages. Claims 7-11 further limit the

oligonucleotides of claim 4 to oligonucleotides wherein the phosphodiester and phosphorothioate linkages are present in ratios in the range of 1:3 to 3:1 or alternate one to one, two to one, one to two, two to two or three to three and wherein the regions of 2'-O-substituted ribonucleotides are connected by phosphorothioate or phosphodiester internucleoside linkages.

Metelev et al. teach hybrid oligonucleotides that comprise a region of 2'-O-substituted ribonucleotides at the termini of a region of deoxyribonucleotides, wherein the regions of 2'-O-substituted ribonucleotides are connected by internucleotide linkages including phosphorothioate or phosphorodiester. Metelev et al. teach their oligonucleotides wherein the nucleotides are linked by a mixture of phosphorothioate and phosphodiester linkages. The oligonucleotides taught by Metelev et al. comprise between 12 and 50 and 17 and 35 nucleotides and wherein the phosphodiester and phosphorothioate linkages are present in ratios in the range of 1:3 to 3:1 or alternate one to one, two to one, one to two, two to two or three to three and wherein the regions of 2'-O-substituted ribonucleotides are connected by phosphorothioate or phosphodiester internucleoside linkages. Metelev et al. do not explicitly teach an embodiment wherein the mixture of phosphorothioate and phosphodiester linkages occurs within the deoxyribonucleotide region of the oligonucleotide.

Ghosh et al. teach phosphorothioate-phosphodiester oligonucleotide co-polymers, including oligonucleotides that have alternating phosphorothioate and phosphodiester linkages with the same pattern as the preferred embodiments disclosed in the instant application and within the ratio of 1:3 to 3:1 and about

1:1. Ghosh et al. discloses embodiments wherein the POPS block include phosphorothioate and phosphodiester bonds alternating in the manner claimed (see for example Table 1). The oligonucleotides taught by Ghosh et al. comprise between 12 and 50 and 17 and 35 nucleotides. Ghosh et al. do not teach a region of 2'-O-substituted ribonucleotides in their phosphorothioate-phosphodiester oligonucleotide co-polymers.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Metelev et al. and Ghosh et al. to make a hybrid oligonucleotide comprising a region of alternating phosphorothioate and phosphodiester linkages, as taught by Ghosh et al., with a region of 2'-O-substituted ribonucleotides, as taught by Metelev et al. because Metelev et al. teach that hybrid oligonucleotides comprising phosphorothioate and phosphodiester linkages and 2'-O-substitued ribonucleotides and deoxyribonucleotides regions have superior properties of duplex formation, Rnase H activation and nuclease resistance which used as an antisense molecule. Ghosh et al. identify phosphorothioate-phosphodiester oligonucleotide co-polymers as the best design for an antisense molecule as it results in the advantages of reduced nuclease stability, specificity and hybridization (see for example, page 31). One of ordinary skill in the art would have been motivated to combine the phosphorothioate-phosphodiester oligonucleotide co-polymer design taught by Ghosh et al. into the hybrid oligonucleotide taught by Metelev et al. to obtain the benefits of antisense design taught by each Ghosh et al. and Metelev et al.

Therefore, the invention of claims 4-6 and 7-11, as a whole, would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Response to Arguments

In response to the rejection of record of claims 4-6 under 35 USC 103(a), as being unpatentable over Metelev et al. in combination with Ghosh et al., set forth in the prior Office action, mailed August 26, 2003, Applicant argues that there is no motivation to combine the cited references. Applicant further argues that there is no reasonable expectation of success to combine the cited references and achieve the instant invention and that the prior art taught way from the claimed invention. These arguments have been fully considered, but not found to be persuasive.

Applicant argues that there is no motivation to combine the teaching of Ghosh et al. and Metelev et al., however, both Ghosh et al. and Metelev et al. teach their modifications for the purpose of creating an improved antisense molecule. " It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[The] idea or combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) See MPEP 2144.06.

Applicant further argues that there was no reasonable expectation of success and that it was only "obvious to try" to make the claimed oligonucleotides. This is not found to be persuasive because Applicant has not provided any reason why the skilled artisan would not have expected to be able to make and or use the oligonucleotides claimed. At the time of the invention, the technology for making oligonucleotides, including modified oligonucleotides as claimed, was well established and routine, as exemplified by the teachings of Ghosh et al. and Metelev et al., and using antisense to inhibit gene expression in a cell in vitro, for example, was also routine. The skilled artisan would have reasonably expected to successfully make and use the claimed oligonucleotides using the methods of synthesis and methods of assaying gene expression well known in the art, as exemplified by Ghosh et al. and Metelev et al.

Applicant argues that there was a teaching in the art against making the claimed combination of modifications. Applicant points to Henry et al., wherein there is a teaching that administering phosphorothioate oligonucleotides to non-human primates results in toxicity. This is not persuasive because the claims are drawn to oligonucleotide compositions, not methods. The claimed oligonucleotides can be used for many other purposes, which Henry et al. does not teach away from. Further, Henry et al. is directed to fully phosphorothioate modified oligos, not combination oligos, which are the subject of the instant claims, and Henry et al. does not teach away from using such oligos but rather teaches caution and suggests further experimentation to design oligonucleotides that avoid the complementation activation experienced with all phosphorothioate

antisense, which would actually suggest making antisense with a different backbone design, as taught by Ghosh et al. and Metelev et al. Ghosh et al. and Metelev et al. each teach that oligonucleotides with combinations of phosphorothioate and phosphodiester backbones overcome problems associated with fully phosphorothioate oligonucleotides.

Applicant further argues unexpected results with their specific oligonucleotides. Applicant points to exhibits that show one oligonucleotide, with one particular pattern of backbone modification, experienced a reduced amount of nuclease stability as compared to an all phosphorothioate version. Applicant states that this oligonucleotide also avoids deleterious immune effects and states other POPS blocks oligonucleotides had similar properties.

These arguments are not found to be persuasive because one oligonucleotide with unexpected results is not sufficient to demonstrate unexpected results for the many different types of oligonucleotides encompassed in the claims. These unexpected results do not address the scope of the claims. Further, it is unclear how the results are unexpected. Applicant shows data for reduced nuclease stability, which would be the logical expected result, but it is unclear that any unexpected reduction in immune response occurred or duplex instability was unexpectedly reduced. Applicant has not provided any data to support their statement or any data by which an assessment can be made as to the unexpected nature of the properties of the claimed oligonucleotides.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
August 9, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER